REMARKS

Claims 1, 6 and 9-11 currently are pending in the application. In view of the following remarks, Applicants believe that all the rejections are in condition for withdrawal and that all pending claims 1, 6 and 9-11 are in condition for allowance.

The Present Invention

The present invention as claimed in claim 1 is directed to a method of enhancing an immune response to an antigen in a mammal comprising administering to the mammal lymphocyte conditioned media (LCM) derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

35 U.S.C. § 103 Rejection of Claims 1 and 9-11

Claims 1 and 9-11 are rejected under 35 U.S.C. § 103(a) as being obvious over Baxevanis et al. in view of Setaluri et al. and Mengozzi et al. In the Advisory Action, the Examiner asserts that Baxevanis discloses that supernatants harvested from stimulated PBMC cultures induce autologous lymphocytes *ex vivo* to display durable anti-tumor cytotoxic response in clinical trials. The Examiner acknowledges that Baxevanis does not disclose the administration of PBMC supernatants with a vaccine of an antigen, but asserts that Baxevanis discloses that activated PBMC results in antigen-specific and antigen-non-specific T-lymphocyte cytotoxicity. The Examiner further asserts that the motivation to modify the anti-CD3 stimulation method taught by Baxevanis is clearly stated in Mengozzi, which discloses that anti-CD3/CD28 antibodies co-immobilized on beads result in maximal cellular replication. The Examiner also asserts that Setaluri is cited to meet the limitations of dosage, routes, and schedule of administration in claims 9-11. The Examiner alleges that Setaluri motivates the combination with Baxevanis because its disclosure of the method of administration can increase the levels of the amount of the therapeutic protein (MAP-2) in cells.

Applicants respectfully request that the rejection be reconsidered and withdrawn for the following reasons.

Baxevanis discloses an *in vitro* method in which whole peripheral blood mononuclear cells (PBMCs) are taken from normal individuals and stimulated with anti-CD3 antibodies. The culture media is added to PBMCs from cancer patients to induce expansion of cytotoxic lymphocytes.

In contrast to the Baxevanis disclosure, the claimed invention is directed to an *in vivo* method of enhancing an immune response to an antigen by using solely naïve T cells cultured with anti-CD3 and anti-CD28 to derive a lymphocyte cultured medium (LCM), which is administered to a mammal in combination with a vaccine. Thus, not only is the starting material

disclosed in Baxevanis generated from a completely different source from the claimed invention, i.e., whole PBMCs, but Baxevanis discloses a completely different method, i.e., activating whole PBMCs solely with anti-CD3. Moreover, the *in vivo* responses produced by the methods of the claimed invention consist of B cell antibody production as a result of administration of LCM in combination with a vaccine to the mammals, with no mention of cytotoxic lymphocyte production, whereas the method of Baxevanis solely results in cytotoxic (T-cell) lymphocyte production. Furthermore, Baxevanis is completely silent with respect to administering a vaccine to an antigen in combination with PBMCs.

With respect to Mengozzi, this reference is non-analogous to the claimed invention. Specifically, Mengozzi is directed to enhancing or inhibiting cell (R5 HIV) replication in infected CD4 T cells, in which the use of high concentrations of CD3/CD28 cross-linking agents results in maximal cellular replication. This is inapposite to the claimed invention, which is directed to immunological responses, i.e., *in vivo* enhancement of the immune system.

With respect to Setaluri, this reference is directed to specific markers for determining the metastatic potential of tumors and, as such, the dosages disclosed in Setaluri would be completely irrelevant to the claimed dosages for administering LCM in combination with a vaccine for enhancing the immune system *in vivo*.

Applicants, therefore, submit that Baxevanis neither teaches nor suggests the claimed invention as claimed in claims 1 and 9-11, and that Mengozzi and Setaluri do not cure the deficiencies of Baxevanis.

Furthermore, one skilled in the art would not be motivated to combine the teaching of Baxevanis, which is concerned with tumor-reactive cytotoxic T-cell lymphocyte production in cancer patients, with that of Mengozzi, which is concerned with cell replication, or with Setaluri, which is concerned with specific markers for determining the metastatic potential of tumors, to derive the claimed invention, which inheres in the unexpected finding that immune responses, specifically antibody B-cell production, to an antigen in a mammal can be significantly enhanced *in vivo* by administering lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

35 U.S.C. § 103 Rejection of Claims 1 and 6

Claims 1 and 6 are rejected under 35 U.S.C. § 103(a) as being obvious over Baxevanis et al. in view of Meidenbauer et al. and Mengozzi et al. The Examiner asserts that Meidenbauer et al. disclose administering a PSA-based vaccine in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) to induce a cellular immune response to human PSA predominantly mediated by T lymphocytes. The Examiner acknowledges that Meidenbauer et al.

do not disclose administering LCM derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads.

As discussed in detail hereinabove, Baxevanis discloses an *in vitro* method in which whole PBMCs are taken from normal individuals and stimulated with anti-CD3 antibodies, in which the media from the culture is added to PBMCs from cancer patients to induce expansion of cytotoxic T-cell lymphocytes. The starting material disclosed in Baxevanis is generated from a completely different source from the claimed invention, i.e., whole PBMCs, and the method is completely different from the claimed invention, i.e., activating whole PBMCs solely with anti-CD3. Moreover, the *in vivo* responses produced by the methods of the claimed invention consist of B cell antibody, production as a result of administration of LCM in combination with a vaccine to the mammals, with no mention of cytotoxic lymphocyte production, whereas the method of Baxevanis solely results in cytotoxic (T-cell) lymphocyte production.

Mengozzi is non-analogous to the claimed invention, as it is directed to enhancing or inhibiting cell (R5 HIV) replication in infected CD4 T cells, in which the use of high concentrations of CD3/CD28 cross-linking agents results in maximal cellular replication. This is inapposite to the claimed invention, which is directed to immunological responses, i.e., *in vivo* enhancement of the immune system.

With respect to Meidenbauer, this reference discloses, as acknowledged by the Examiner, administering a PSA-based vaccine in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) to induce a cellular immune response to human PSA predominantly mediated by T lymphocytes. The Examiner further acknowledges that Meidenbauer et al. do not disclose administering LCM derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads.

The disclosure of Meidenbauer is completely different from the claimed invention, which is directed to administering a vaccine to an antigen in combination with LCM derived solely from naïve T-cells cultured with antiCD3- and CD28-coated beads,
in which there is no mention whatsoever of using GM-CSF. Furthermore, the *in vivo* responses produced by the methods of the claimed invention consist of B cell antibody production and not T cells as disclosed in Meidenbauer.

Applicants, therefore, submit that Baxevanis neither teaches nor suggests the claimed invention as claimed in claims 1 and 9-11, and that Meidenbauer and Mengozzi, do not cure the deficiencies of Baxevanis.

Furthermore, one skilled in the art would not be motivated to combine the teaching of Baxevanis, which is concerned with tumor-reactive cytotoxic T-cell lymphocyte production in

cancer patients with that of Meidenbauer, which is concerned with administering a PSA-based vaccine in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) to induce a cellular immune response to human PSA predominantly mediated by T lymphocytes, or with Mengozzi, which is concerned with cell replication, to derive the claimed invention, which inheres in the unexpected finding that immune responses, specifically B cell antibody production, to an antigen in a mammal can be significantly enhanced *in vivo* by administering lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims 1, 6 and 9-11 in the present application are patentable over the cited prior art. Accordingly, reconsideration and withdrawal of the rejections and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

Gwen R. Acker Wood, Ph.D., J.D.
Attorney for Applicants
Registration Number 51,027

Telephone: 412-566-6085
E-mail Address: gwood@eckertseamans.com